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Mass Spectrometry-Based Intraoperative Tissue Identification in Neurosurgery

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Disclosure

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Regarding surgery for malignant brain tumors, it is agreed upon by most neurosurgeons and supported by strong evidence that gross-total resections (GTRs) are associated with longer survival. One of the main challenges in achieving the largest extent of resection without causing damage to the surrounding healthy brain parenchyma is the distinction between tumor and normal brain. This distinction is especially difficult in primary brain tumors, which often show a diffuse growth pattern resulting in a transitional zone at the tumor margins where malignant and normal cells are intermingled. In cases where visual identification of tumor is not possible, intraoperative frozen sections are the current gold standard. However, they are time-consuming (20-40min) and therefore cannot be repeated as often as one might require this information. In addition, the results are often unspecific or inconclusive. Therefore, much effort has been invested in the development of technologies that might improve the extent of tumor resection. In daily practice, neurophysiological monitoring, neuronavigation, intraoperative magnetic resonance imaging (ioMRI), intraoperative ultrasound (ioUS) and 5-aminolevulinic acid (5-ALA) are the most frequently used ones.

Recently, a new technique called rapid evaporative ionization mass spectrometry (REIMS) has been put forward by Balog et al. [2]. The authors analyzed the “smoke” created by electrosurgery (either monopolar or bipolar) by means of REIMS. They coined the term “intelligent knife” (iKnife) for this coupling of electrosurgery and mass spectrometry which allows near-real-time characterization of human tissue. In a first step, Balog et al. analyzed 302 different human tissue samples in the laboratory, resulting in a database of tissue-specific mass spectra with 1624 cancerous and 1309 noncancerous entries. Afterwards, the technology was translated into the operative theater and mass spectra from 81 surgical resections were analyzed. This study represents the first-in-human application of this novel technology. The results

of both the *ex vivo* and the *in vivo* analyses are convincing. Out of the 2933 database entries derived from *ex vivo* experiments, a total of 254 spectra originated from brain tissue (49 spectra from 6 glioblastoma samples, 99 spectra from 10 metastases, 87 spectra from other brain tumors, and 19 spectra from healthy grey or white matter). Leave-one-patient-out cross-validation was used and shows high rates for glioblastomas (83.7%) and metastases (92.3%); the rate of incorrectly classified tumor specimens as healthy tissue was 2.0% for glioblastoma and 7.7% for metastases.

Regarding the intraoperative (*in vivo*) analysis of surgical specimen, the authors analyzed a total of 864 spectra acquired from 81 patients. When compared to the postoperative histopathological diagnosis, the overall sensitivity was 97.7% and the specificity was 96.5% (classification cancer vs. healthy). Neurosurgical specimen (11 brain tumors, not specified further by the authors) were detected with a sensitivity and specificity of 100%. The procedure of sampling the smoke, transfer to the mass spectrometer, analysis and feedback to the surgeon took 0.7 to 2.5 seconds. When compared to frozen sections (20-40min) this new technology does allow frequent testing and potentially shortens the entire surgery duration.

Despite discriminating between tumor and healthy tissue, REIMS was also successful in differentiating different grades of a tumor (such as WHO grades of brain tumors) as well as in differentiating metastases from distinct primary tumors.

Balog et al. used REIMS coupled to a monopolar as well as to a bipolar electrosurgery device. It seems clear that the bipolar setup is the one that is relevant to the neurosurgeon.

During tumor resections in neurosurgery an alternative to electrosurgery, ultrasonic disintegration and aspiration of tumor tissue, is frequently used. This mode of tumor resection does not produce any smoke than can be analyzed. However, an off-line

method using frozen material from the effluent of the ultrasonic aspiration device for desorption electrospray ionization mass spectrometry (DESI-MS) has been suggested in a proof-of-concept study [1] and another group was able to perform real-time analyses during ultrasonic aspiration by coupling a cavitron ultrasonic surgical aspirator (CUSA) to a Venturi easy ambient sonic – spray ionization (V-EASI) system [3]. However, the results of the latter setup are only presented for ex vivo experiments and specific results for sensitivity and specificity are not given.

In our opinion, the *in vivo* tested and highly sensitive and specific method REIMS could be combined with surgical aspirators (even with those that do not use ultrasonic tissue disintegration) by adding a bipolar electrosurgery device to the tip of the aspirator that can be advanced by the surgeon (see Figure 1). The smoke produced during bipolar electrocautery can then easily be used for REIMS-based analysis as introduced by Balog et al.

Remaining questions are, whether a feasible cut-off value of tumor cell concentration can be defined at the tumor margins of diffusely infiltrating tumors and whether REIMS-guided tumor resection results in improved survival. Since tumor cells in highly malignant brain tumor such as glioblastoma can be found centimeters away from the main core of the lesion, it is virtually impossible to resect the entire tumor cell population. Therefore, a reasonable cut-off level of tumor-load at the tumor margin as detected by REIMS has to be defined – a trade-off between maximal resection and preservation of healthy brain parenchyma.

Nevertheless, this new technology could be a milestone in brain tumor surgery. We are looking forward to see the first results of wide-spread clinical use.

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2. Balog J, Sasi-Szabo L, Kinross J, Lewis MR, Muirhead LJ, Veselkov K, Mirnezami R, Dezso B, Damjanovich L, Darzi A, Nicholson JK, Takats Z (2013) Intraoperative tissue identification using rapid evaporative ionization mass spectrometry. *Science translational medicine* 5 (194):194ra193. doi:10.1126/scitranslmed.3005623
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Figure 1

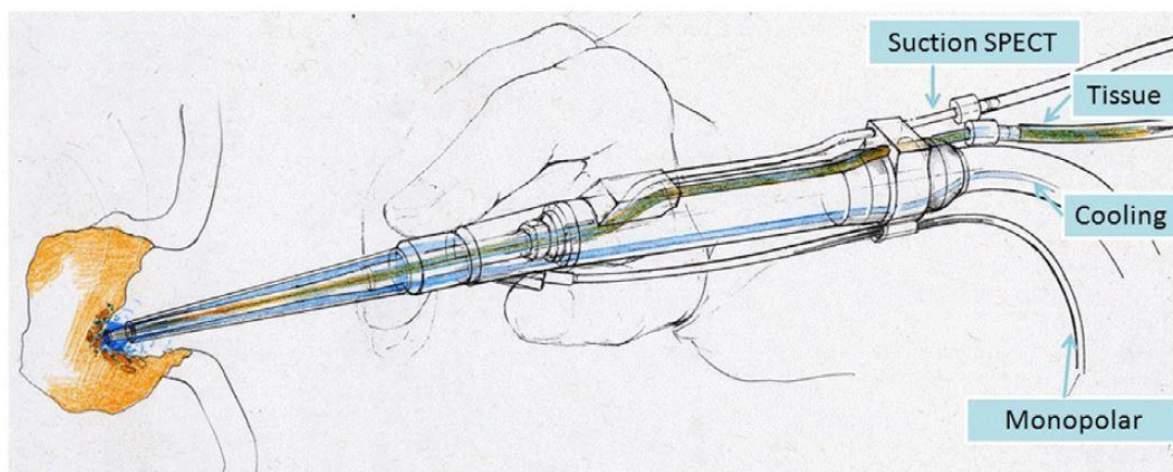


Figure 1. Use of a monopolar electrosurgery device attached to the tip of the aspirator to combine rapid evaporative ionization mass spectrometry with surgical aspiration. SPECT, single photon emission computed tomography.